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<b>(21) International Application Number:</b> PCT/GB97/00496 <b>(22) International Filing Date:</b> 24 February 1997 (24.02.97) <b>(30) Priority Data:</b> 9603945.8                      24 February 1996 (24.02.96)                      GB <b>(71) Applicant (for all designated States except US):</b> THE UNIVERSITY COURT OF THE UNIVERSITY OF ST. ANDREWS [GB/GB]; College Gate, St. Andrews, Fife KY16 9AJ (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GANI, David [GB/GB]; Bois-Fleuris, Brownhills Farm Steading, Crail Road, St. Andrews, Fife KY16 8PL (GB). AKHTAR, Mahmoud [GB/GB]; 4 Reid Gardens, St. Andrews, Fife KY16 8XR (GB). KROLL, Friedrich, Erich, Karl [DE/GB]; 19 Forrest Street, St. Andrews, Fife KY16 8HR (GB). SMITH, Colin, Forbes, MacDonald [GB/GB]; 26 Lamond Drive, St. Andrews, Fife KY16 8BE (GB). <b>(74) Agent:</b> MURGITROYD & COMPANY; 373 Scotland Street, Glasgow G5 8QA (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> A MICROREACTOR  <b>(57) Abstract</b> <p>A microreactor (20) for the synthesis of chemical compounds includes a container having a body section (21). Entry pores are provided to permit fluid to enter the container and a visual identification device is provided to enable visual identification of the microreactor (20).</p> <div data-bbox="808 1136 1377 1480"></div>		

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1     "A Microreactor"

2

3     The invention relates to a microreactor, and especially  
4     a microreactor for synthesising chemical compounds.

5

6     Recent trends in the area of drug development,  
7     biotechnology and chemical research have moved towards  
8     producing large arrays of related molecules using  
9     combinatorial (or permutational) synthesis. These new  
10    techniques are potentially capable of yielding  
11    libraries of millions of compounds which can be  
12    screened, if a suitable assay is available, to identify  
13    the required properties, for example biological  
14    activity. The new methods have advantages because only  
15    a relatively small number of chemical reaction vessels  
16    need to be used, compared to the traditional methods in  
17    which a single compound is sequentially processed  
18    through various chemical transformations, usually one  
19    reaction step at a time. The new method, combinatorial  
20    synthesis, relies on the fact that under suitable  
21    conditions several compounds can be converted into  
22    several new products using a single reaction vessel.

23

24    The problems with combinatorial chemistry are manifold.  
25    First, reaction chemistry needs to be irreversible,

1 such that each of the starting materials in the mixture  
2 is converted to a new product. Second, at the present  
3 time it is only feasible to perform combinatorial  
4 chemistry for large libraries in the "solid-phase",  
5 that is where the starting materials are covalently  
6 bonded to a polymeric support, which is usually cross-  
7 linked polystyrene. The advantages of solid-phase  
8 synthesis are that the products do not need to be  
9 purified by, for example, solvent extraction,  
10 distillation, recrystallisation or chromatography but  
11 rather are retained on the solid medium by washing away  
12 the excess reagents and impurities. Thus, in solid-  
13 phase synthesis (SPS) it is necessary to confine the  
14 polymeric support so that it too is not washed away.

15  
16 The third problem concerns the deconvolution of the  
17 library which essentially requires identifying the  
18 chemical structure of the molecule, within the mixture,  
19 that shows the required biological activity or other  
20 desired property. Clearly, when one is dealing with  
21 mixtures of compounds, where the polymeric support for  
22 one compound looks identical to another requires the  
23 resynthesis of partial libraries of ever decreasing  
24 size, coupled with assay in order to identify the  
25 active material. This method of deconvolution is time  
26 consuming and unnecessarily clumsy. Another way of  
27 effecting deconvolution is to tag the polymeric support  
28 with chemicals which can be used to decode the  
29 synthetic chemical history of the particular particle  
30 of polymeric support, independently to being able to  
31 carry out an activity assay on the material attached to  
32 the support. Such methods have been described in the  
33 literature. Since typical particles of polymeric  
34 support are referred to as "resin beads" and are  
35 commercially available in the size 90-400 microns,  
36 deconvolution by such methods is a fiddly job requiring

1 accurate and expensive instrumentation.

2

3 The fourth problem concerns checking the efficiency of  
4 the chemical synthesis and, in essence, this is a  
5 problem of scale. Individual beads possess, at most,  
6 only a few nanomoles of material attached to them and  
7 thus it is extremely difficult to check either the  
8 efficiency of the synthesis or the purity of the  
9 synthetic product. In highly sensitive biological  
10 screening assays this can be a very serious problem as  
11 the impurity could be responsible for a positive  
12 result. The best way to overcome this last problem is  
13 to perform syntheses on a larger scale such that some  
14 material can be put aside for characterisation and  
15 analysis. While this solution offers very many  
16 advantages, the practice of larger scale combinatorial  
17 syntheses requires the design and use of microreactors.  
18 To date, only two reports of the use of microreactors  
19 (or porous capsules) for solid-phase synthesis on a  
20 polymeric support have been described, and the authors  
21 supplied little information on the design of the  
22 microreactors. The main purpose of the reports was to  
23 describe the incorporation of an addressable microchip  
24 into the microreactors which could be written to and  
25 read using radio waves. This elegant idea does require  
26 the microreactors to be of a size large enough to  
27 contain the addressable chip, which in itself is not a  
28 problem, but again demands the use of sophisticated and  
29 expensive equipment for the identification of  
30 individual compounds.

31

32 In accordance with a first aspect of the present  
33 invention, a microreactor for synthesis of chemical  
34 compounds comprises a container comprising a body  
35 section; entry means to permit fluid to enter the  
36 container; and a visual identification device to enable

1 visual identification of the microreactor.

2

3 The term "microreactor" as used herein means a  
4 container comprising a material which is permeable to  
5 fluids. The container may enclose a solid material or  
6 particles on or with which reaction occurs, and the  
7 container is impermeable to the solid material or  
8 particles. Alternatively, the material of the  
9 container itself may comprise a chemically  
10 functionalised polymer on or with which reaction  
11 occurs. This can be referred to as a "bonded"  
12 microreactor.

13

14 The microreactor may further comprise a closure and the  
15 body section may have an opening, the closure being  
16 adapted to close the opening, and fluid being able to  
17 enter the container through the entry means when the  
18 opening is closed by the closure.

19

20 Alternatively, the body section may comprise a material  
21 which comprises a polymeric support on or with which  
22 reaction occurs. Typically, the polymeric support may  
23 be chemically functionalised polystyrene and may be in  
24 the form of a porous, frit or sintered material.

25

26 In accordance with a second aspect of the present  
27 invention, a method of identifying a microreactor for  
28 synthesis of chemical compounds comprises attaching a  
29 visual identification device to the microreactor to  
30 enable the microreactor to be visually identified.

31

32 An advantage of the invention is that it permits  
33 deconvolution of a library of synthesised molecules by  
34 visual identification of a microreactor.

35

36 Preferably, the visual identification device may

1 comprise a character and/or a colour. Typically, the  
2 character may be an alphanumeric character.

3

4 Typically, the visual identification device may be  
5 attached to the external surface of the container.  
6 However, alternatively, the visual identification  
7 device may be inserted into the container or may be  
8 incorporated into the material of the container, which  
9 may be the body section and/or the closure.

10

11 The closure may be removable or non-removable from the  
12 opening.

13

14 Typically, each microreactor may comprise a number of  
15 visual identification devices, which may be different  
16 or identical.

17

18 The visual identification devices may be attached to  
19 the microreactor prior to the microreactor being used  
20 for synthesis of chemical compounds. Alternatively,  
21 the visual identification devices may be attached as  
22 appropriate before or after each stage in the synthesis  
23 procedure, one at a time or several at a time.

24

25 The visual identification device may be of a size to be  
26 visually identified by humans, or alternatively may be  
27 identified by robotics or another type of machine.

28

29 Typically, a separate visual identification device is  
30 provided for each chemical in which the microreactor is  
31 immersed during synthesis.

32

33 In one example of the invention, the body section may  
34 have two openings and two removable closures, one  
35 closure for each opening. Typically, in this example  
36 of the invention, the body section may be tubular with

1 the openings provided at each end of the tubular body  
2 section.

3

4 In a second example of the invention, there may be just  
5 one opening in the body section, which may be  
6 cylindrical in form.

7

8 In the case of bonded microreactors which themselves  
9 consist of chemically functionalised frit glass or frit  
10 or foamed polymer, there do not need to be openings for  
11 loading and unloading of resin, as the chemically  
12 reactive groups would be retained within the bonded  
13 matrix itself.

14

15 Where the visual identification device is attached to  
16 the outer surface of the container, the device may  
17 comprise a ring shaped member which is fitted over the  
18 body section and visual identification may be provided  
19 by a colour of the member and/or by characters on the  
20 surface of the member.

21

22 Alternatively, the visual identification device may be  
23 inserted into holes or apertures in a side wall of the  
24 container. For example, the visual identification  
25 device may comprise a peg or bead which fits into and  
26 is held in the hole or aperture.

27

28 Preferably, the entry means is provided by apertures in  
29 the side walls of the container. The side walls may  
30 comprise frit material, a perforated polymer material  
31 or a mesh. It is possible that a combination of these  
32 materials could be used. Examples of suitable frit  
33 materials are frit glass, frit polyethylene, frit  
34 polypropylene and frit polytetrafluoroethylene (PTFE).

35

36 The closure may be attached to the body section by



1 being a push fit into the opening, by being threadedly  
2 connected to the body section or attached by an  
3 adhesive.

4  
5 Typically, for biological applications, the  
6 microreactors may have a length of approximately 7-  
7 10mm, and internal width of 3.5-7mm and an outside  
8 width of 4-10mm. Typically, the microreactors are for  
9 use with standard commercially available polymer beads  
10 of 90-400 microns for solid support in the solid phase  
11 synthesis.

12  
13 However, these dimensions should not be considered as  
14 being limiting and larger microreactors or smaller  
15 microreactors may be constructed for other  
16 applications. For example larger microreactors may be  
17 constructed and used for non-biological applications.

18  
19 Typically, the microreactor and the visual  
20 identification device are composed of cheap inert  
21 material and the selection of the materials is dictated  
22 by the intended chemistry, ie only compatible materials  
23 are used, eg glass is not used with aqueous  
24 hydrofluoric acid and non-resistant polymers are not  
25 used with organic solvents.

26  
27 Examples of a microreactor in accordance with the  
28 invention will now be described with reference to the  
29 accompanying drawings, in which:-

30  
31 Fig. 1 is a cross sectional view through a first  
32 example of a microreactor;

33 Fig. 2 is a cross sectional view through a second  
34 example of a microreactor;

35 Fig. 3 is a perspective view of a third example of  
36 a microreactor;

1           Fig. 4 is a plan view of the microreactor shown in  
2           Fig. 3;  
3           Fig. 5 is a front view of the microreactor shown  
4           in Fig. 3;  
5           Fig. 6 is a back view of the microreactor shown in  
6           Fig. 3;  
7           Fig. 7 is an exploded side view of a fourth  
8           example of a microreactor;  
9           Fig. 8 is a side view of the microreactor of Fig.  
10          7 assembled; and  
11          Fig. 9 is a flow diagram illustrating how twenty-  
12          seven microreactors may be used to synthesise  
13          twenty-seven compounds from three suitably  
14          functionalised starting compounds.  
15  
16          Fig. 1 shows a first example of a microreactor 1 which  
17          comprises a polymer tube having 70 micron perforations  
18          in the wall of the tube 2. At each end of the tube 2  
19          is an end cap 3. The material from which the tube 2  
20          and end caps 3 are manufactured is inert with the  
21          compounds into which the microreactor 1 is to be  
22          immersed. Located within the microreactor 1 are a  
23          number of polymer beads 4 for solid support in solid  
24          phase synthesis. The polymer beads have a diameter  
25          which is greater than 70 microns.  
26  
27          A second example of a microreactor 5 is shown in Fig.  
28          2. The microreactor 5 comprises a container body  
29          section 6 having an open end 7 which is closed by a  
30          removable lid 8. The container body section 6 and the  
31          removable lid 8 are both manufactured from frit glass  
32          and the frit glass is chosen to be inert with the  
33          compounds in which the microreactor 5 is to be  
34          immersed. However, any other suitable frit material  
35          may be used. The microreactor 5 also contains a number  
36          of polymer beads for solid support in solid phase

1 synthesis.

2

3 Figs. 3 to 6 show a third example of a microreactor 20  
4 which is manufactured from a frit material. This may  
5 be frit glass, frit polyethylene, frit  
6 polytetrafluoroethylene or any other suitable frit  
7 material. A "suitable frit material" is any frit  
8 material which is inert with the chemicals into which  
9 the microreactor 20 is to be immersed.

10

11 The microreactor 20 consists of a cylindrical body  
12 section 21 which has a hole 22 drilled into the curved  
13 surface of the cylindrical body section 21. Hole 22  
14 has polymer beads inserted into it before the hole 22  
15 is plugged by a plug 23. Around the curved surface of  
16 the body section 21 a number of small holes 24 are  
17 drilled. These holes permit small coloured pegs to be  
18 attached to the microreactor 20 by being pushed into  
19 the holes 24.

20

21 After the hole 22 has been plugged by the plug 23, the  
22 plugged hole 22 forms a reaction chamber into which  
23 chemical fluids may enter through the holes in the frit  
24 material from which the body section 21 is formed. The  
25 plug 23 may be any suitable inert material, such as an  
26 inert polymer.

27

28 As an alternative to the microreactor 20, the  
29 microreactor could be manufactured from porous or frit  
30 perfluoroalkyl sulphonic acid resin, such as Nafion  
31 (trade mark) manufactured by Du Pont, so that the  
32 material of the microreactor itself forms the polymeric  
33 support. In addition, or alternatively, other  
34 chemically functionalised sintered, frit or porous  
35 polymers or composites could be used to form the  
36 microreactor.

1 In this example, the microreactor would not have the  
2 reaction chamber 22 or the closure 23 and would be a  
3 body of material porous or frit material. However, the  
4 holes 24 for the coloured pegs would still be present.  
5 The reactions then take place on or with the material  
6 of the microreactor itself.

7  
8 Figs. 7 and 8 show a fourth example of a microreactor  
9 30. Fig. 7 is an exploded side view of the  
10 microreactor 30 showing the components of the  
11 microreactor 30. The microreactor 30 has a tubular  
12 glass body 31 which has an external screw thread  
13 formation 32. The body 31 is hollow and two sealing  
14 rings 33 and a frit glass end closure 34 are secured to  
15 each end of the glass body 31 by an end cap 35. The  
16 end caps 35 are internally threaded so that they screw  
17 onto the thread 32 on the body 31.

18  
19 If the end closures 34 are of a frit material, such as  
20 a plastic, it would not be necessary to use the sealing  
21 rings 33.

22  
23 In use, one end cap 35, end closure 34 and sealing  
24 rings 33 are secured to one end of the body 31. The  
25 polymer beads may then be placed in the body 31 through  
26 the other open end. The open end is then closed using  
27 the other end cap 35, end closure 34 and sealing rings  
28 33.

29  
30 The visual identification devices for the microreactor  
31 30 may be moulded into the end caps 35, which may be  
32 moulded from a plastics material. In addition, it is  
33 possible that the end caps 35 and/or body 31 may be  
34 individually colour coded.

35  
36 In this example the body 31 is solid glass and not frit

1 glass.

2

3 Fig. 8 shows the assembled microreactor 30. In the  
4 microreactor 30, the fluids enter the microreactor  
5 through the end closures 34 which are of a frit  
6 material, and therefore permeable to fluids but not to  
7 the polymer beads placed inside the microreactor 30.

8

9 Both frit glass tubes and rectangular chambers and  
10 perforated polymer tubes and meshes with appropriate  
11 lids were used as microreactors in the synthesis of  
12 small peptide libraries. Standard commercially  
13 available polymer beads 4 of 90-400 microns were used  
14 for the solid support in the solid phase synthesis  
15 (SPS). Essentially, the dimensions of the  
16 microreactors range from a length of 7-10mm, with an  
17 internal diameter of 3.5-7mm, and an outside diameter  
18 of 4-10mm, depending on the material. The walls of  
19 frit glass tube need to be thicker to provide  
20 mechanical strength. The lids 3, 8 of the  
21 microreactors 1, 5 and the plug 23 of the microreactor  
22 20 are resistant polymer or frit glass and can be  
23 colour coded as part of the visually addressable  
24 system. The microreactors 1, 5, 20 themselves can also  
25 be colour coded or marked with the appropriate alpha-  
26 numeric or icon, or with multiple visual  
27 identifications. Larger microreactors can be  
28 constructed for non-biological applications using the  
29 same material and protocols outlined here.

30

31 The microreactors used were pre-labelled, that is the  
32 colours and alpha-numerics were already associated with  
33 each of the microreactors such that the chemical  
34 synthesis was programmed by the visual identification  
35 marks. In principle, this method offers no advantages  
36 or disadvantages in identification compared with

1 tagging the microreactors after each cycle of the  
2 synthesis. However, pre-labelled microreactors could  
3 be used in programmed robotic synthesis, where the  
4 machine or human readable identification is used to  
5 determine which vessel the microreactor is placed into  
6 for the next step. Another advantage is that  
7 microreactors could be manufactured and supplied in a  
8 coded form for the user to predetermine what each  
9 element of the code will mean in the synthesis of the  
10 chemical libraries. This also saves the user from  
11 needing to tag the microreactor after each step.  
12 Moreover, precision machine labelled microreactors have  
13 the potential to be smaller than those described above  
14 where for human visualisation, as opposed to robotic  
15 identification, the microreactor is read using a  
16 magnifying glass, typically of the type used by  
17 electronics engineers for identifying resistors and  
18 chips etc.

19  
20 The limit of the number of sets of colours,  
21 alphanumerics, etc that can be read easily on the  
22 microreactors described above is six, without the aid  
23 of a magnifying glass. This number could be increased  
24 to twelve by precision manufacture of the microreactors  
25 for visual identification using a magnifying glass.  
26 However, in practise, twelve represents the number of  
27 actual synthetic steps (not counting chemical  
28 activation and protection and deprotection steps which  
29 support the synthetic chemistry) and twelve is probably  
30 beyond the need of any potential application other than  
31 bioactive peptide synthesis. The structural  
32 (molecular) diversity is limited by the visualisation  
33 method. For example, there are ten easily  
34 distinguishable colours and if all ten are used for  
35 each of six syntheses steps there are  $10^6$  individually  
36 addressable microreactors. For easily distinguishable

1 letters (of which there are 24, not counting Greek  
2 letters) there are  $24^6 = 191$  million addressable  
3 microreactors. For a two digit numeric labelling  
4 strategy there are  $9.4148 \times 10^{11}$  individually  
5 addressable microreactors. In practise these numbers  
6 are much larger than those required and typically  
7 libraries of microreactors would be 9-10,000 in size.  
8 Where the overall volume of each microreactor is 0.25-  
9 0.75 cm<sup>3</sup>. a library of 10,000 compounds could be  
10 prepared easily in conventional laboratory scale  
11 equipment. Note that for a diversity factor of 10, ten  
12 separate reactions on 1000 compounds in 1000  
13 microreactors would be performed in the last step to  
14 give a library of 10,000 compounds. 1000 microreactors  
15 would fit inside a vessel of 1000-2000 cm<sup>3</sup> and leave  
16 plenty of room for the solvent and  
17 mixing/heating/cooling and sensing equipment. Typical  
18 large scale laboratory equipment has a maximum capacity  
19 of 10,000 cm<sup>3</sup>. Vessels larger than this require special  
20 facilities.

21  
22 In a typical but non-restrictive protocol for peptide  
23 library or other compound library synthesis, a small  
24 amount of pre-swollen commercially available resin for  
25 solid phase peptide synthesis is added to the pre-  
26 labelled microreactor as a slurry in dimethylformamide  
27 such that the microreactor is half-full or less. A  
28 small glass bead or stirring magnet may be added to  
29 ensure thorough mixing. The microreactor, and any  
30 others which are to be processed, are placed in the  
31 main reaction vessel and are drowned in a solution of  
32 solvent eg dimethylformamide containing the appropriate  
33 reagents for either synthesis or deprotection in the  
34 usual way. The microreactors are physically agitated to  
35 ensure that each resin bead is exposed to the reagent  
36 solution. The microreactors are then transferred to

1 new appropriate reaction vessels, together with other  
2 microreactors, as dictated by the visually addressable  
3 labels for further cycles of deprotection of synthesis.  
4 The entire process is repeated until the synthesis and  
5 deprotection is complete. The library of labelled  
6 microreactors is now ready for solid phase assay (on  
7 the polymer bead) where individual beads are removed to  
8 prepare a library or sub-library of beads of known  
9 composition. If solution phase assays are to be  
10 performed, the compounds are obtained by un-linking the  
11 polymer resin support. This can be performed either on  
12 the entire contents of any or all of the individual  
13 microreactors, or on just a portion of the contents.  
14 Unlinking is performed in the usual way. In our  
15 experiments we used Fmoc peptide chemistry and removed  
16 the compounds from the resin using trifluoroacetic  
17 acid. The purity and structure of the library members  
18 was assessed by nmr spectroscopy. Note that for  
19 unlabelled microreactors, one identification tag (eg a  
20 thin inert polymer ring or peg of a given colour or  
21 marked with a specific alphanumeric or icon) would be  
22 added either prior to, or, immediately after placement  
23 in a reaction vessel for every synthesis.

24  
25 In the case of bonded microreactors composed of porous  
26 functionalised polymer, for example, perfluoroalkyl  
27 sulphonic acid or carboxylic acid resins such as Nafion  
28 or those manufactured by Asahi or Dow, the acid groups  
29 would be activated to load appropriate nucleophilic  
30 linker groups, for example, 3-aminobenzyl alcohol to  
31 give a chemical reaction surface similar to that for  
32 commercially available resins.

33  
34 To illustrate how the visually interrogatable coding  
35 would work in the construction of a combinatorial  
36 library using permutational organic synthesis in



1 addressable microreactors (POSAM), consider a library  
2 10 of twenty-seven compounds made up from three  
3 structural moieties called A, B and C (see Fig. 9).  
4 Twenty-seven microreactors 11 are provided. In the  
5 first cycle of the reaction nine microreactors 11 are  
6 reacted with compound A, nine with B and nine with C,  
7 in separate vessels, to load the polymeric beads in the  
8 microreactors 11 with compounds A, B and C  
9 respectively. The microreactors 11 from each of the  
10 three vessels are then tagged with a visual  
11 identification mark such that the microreactors 11  
12 loaded with A, B and C can be discriminated.

13  
14 In the second cycle of synthesis, three of the  
15 microreactors 11 containing compound A, three  
16 containing B and three containing C are then reacted  
17 with compound A. When the reaction is complete the  
18 microreactors 11 are labelled with a further visually  
19 identifiable tag. Nine further microreactors 11  
20 containing A, B and C (three of each) are then reacted  
21 with compound B and then tagged and the remaining nine  
22 microreactors 11 containing A, B and C are then reacted  
23 with compound C and then tagged. Thus there are now  
24 three sets 12 of nine differentially labelled  
25 microreactors containing the compounds AA, BA, CA, AB,  
26 BB, CB, AC, BC and CC (see Fig. 9).

27  
28 In a third cycle, one set of the nine compounds is  
29 reacted with compound A, and then tagged and a further  
30 set of nine reacted with compound B, and then  
31 differentially tagged and finally, the last set of nine  
32 compounds is reacted with compound C and then tagged.  
33 This gives a final library of twenty-seven different  
34 compounds attached to the polymer support inside the  
35 twenty-seven microreactors 11 which are all  
36 individually distinguishable merely by looking at them.

1 The visual identification of microreactors also ensures  
2 that no mistakes are made during various cycles of  
3 library synthesis and avoids the statistical problems  
4 generated in the split and mix strategy that is used  
5 when dealing directly with the indistinguishable  
6 polymeric beads. If the synthetic efficiency of the  
7 chemical process needs to be interrogated, it is either  
8 possible to open up a microreactor and remove some of  
9 the material for analysis or to include extra identical  
10 microreactors visually tagged in the appropriate manner  
11 which are removed during the synthetic procedure,  
12 specifically for analysis.

13  
14 The protocols described are suitable for a wide range  
15 of chemistries with reactors of a small size, as  
16 described here, up to quite large sizes eg 20 cm<sup>3</sup> per  
17 reactor. In industry and with special vessels even  
18 larger reactors could be used. Clearly, the larger the  
19 reactor the more easily it can be visually addressed.  
20 This patent should cover any confined solid support  
21 chemical reactor used to generate libraries of  
22 compounds greater than four members in two or more  
23 synthetic cycles either sequentially or simultaneously  
24 in larger reaction vessels where reactors are addressed  
25 by any visual interrogation system employing colour,  
26 alphabetic, numeric bar-coding or icon based system.

1     CLAIMS

2

3     1.    A microreactor for synthesis of chemical compounds  
4     comprising a container comprising a body section; entry  
5     means to permit fluid to enter the container; and a  
6     visual identification device to enable visual  
7     identification of the microreactor.

8

9     2.    A microreactor according to claim 1, wherein the  
10    body section comprises a body of material, the material  
11    comprising a polymeric support on or with which  
12    reaction occurs.

13

14    3.    Apparatus according to claim 1, wherein the body  
15    section has an opening and the container further  
16    comprises a closure adapted to close the opening; and  
17    the entry means permits fluid to enter the container  
18    when the opening is closed by the closure.

19

20    4.    A microreactor according to any of the preceding  
21    claims, wherein the visual identification device  
22    comprises a character and/or a colour.

23

24    5.    A microreactor according to claim 4, wherein the  
25    character is an alphanumeric character.

26

27    6.    A microreactor according to any of the preceding  
28    claims, wherein the visual identification device is  
29    attached to the external surface of the container.

30

31    7.    A microreactor according to any of the preceding  
32    claims, wherein the visual identification device is  
33    incorporated into the material of the container.

34

35    8.    A microreactor according to any of the preceding  
36    claims, wherein a microreactor comprises a number of

1 visual identification devices.

2

3 9. A microreactor according to any of the preceding  
4 claims, wherein the entry means is provided by  
5 apertures in the side walls of the container.

6

7 10. A microreactor according to claim 9, wherein the  
8 side walls of the container are porous.

9

10 11. A microreactor according to any of the preceding  
11 claims, wherein the visual identification device is  
12 inserted into holes or apertures in a side wall of the  
13 container to attach the visual identification device to  
14 the container.

15

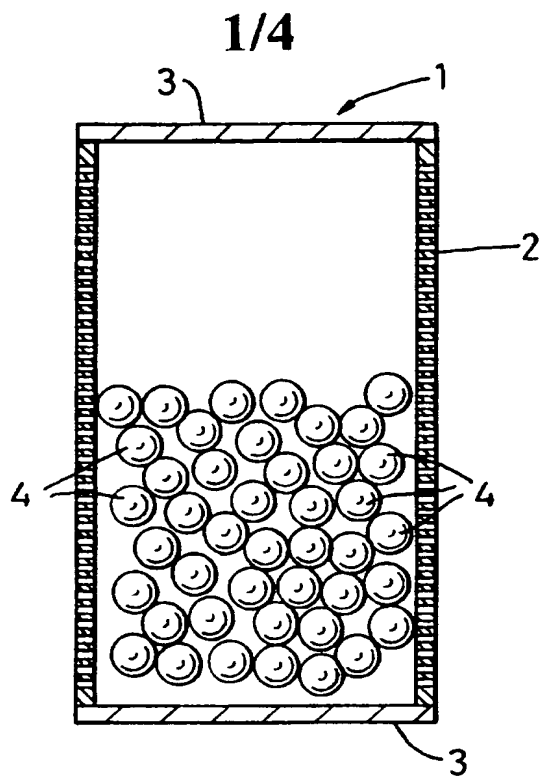
16 12. A method of identifying a microreactor for  
17 synthesis of chemical compounds comprises attaching a  
18 visual identification device to the microreactor to  
19 enable the microreactor to be visually identified.

20

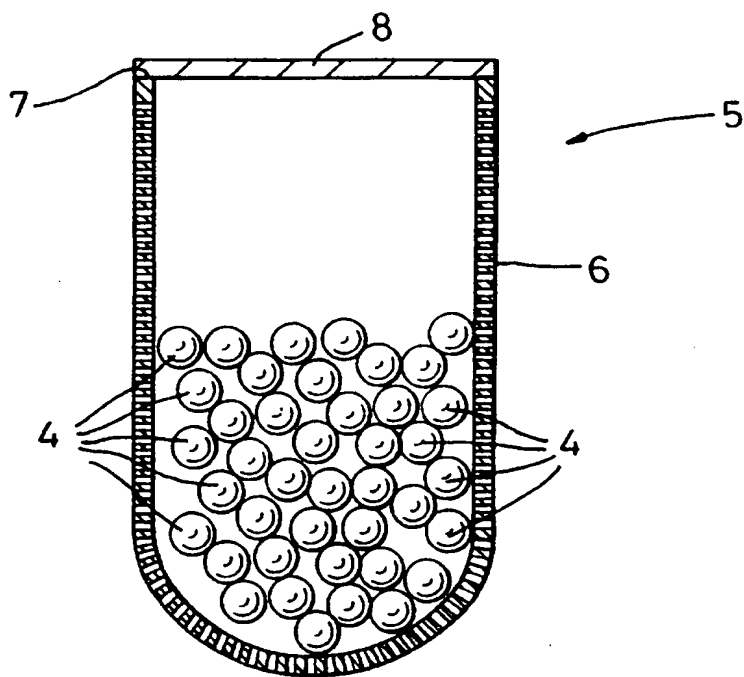
21 13. A method according to claim 12, wherein the visual  
22 identification devices are attached to the microreactor  
23 prior to the microreactor being used for synthesis of  
24 chemical compounds.

25

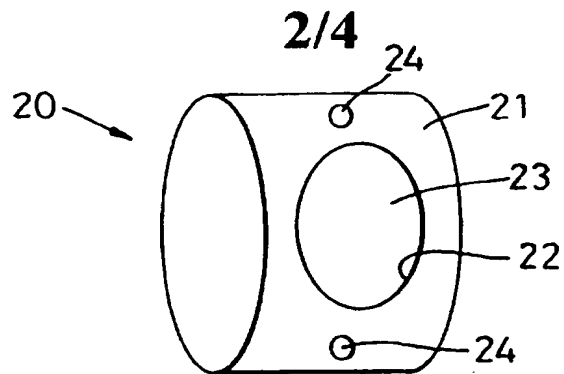
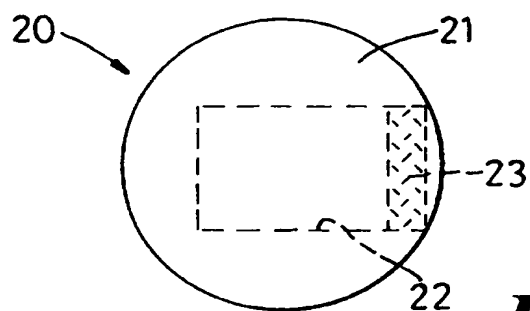
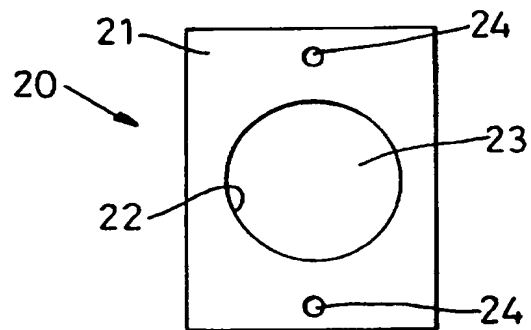
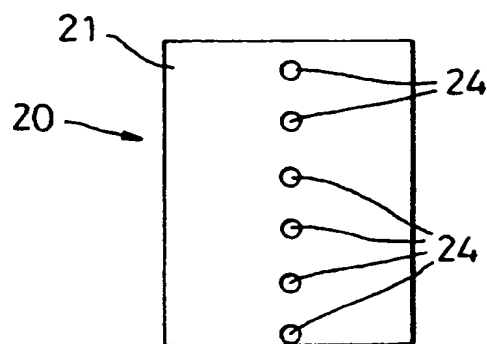
26 14. A method according to claim 12, wherein the visual  
27 identification devices are attached where appropriate  
28 before or after each stage in the synthesis procedure.



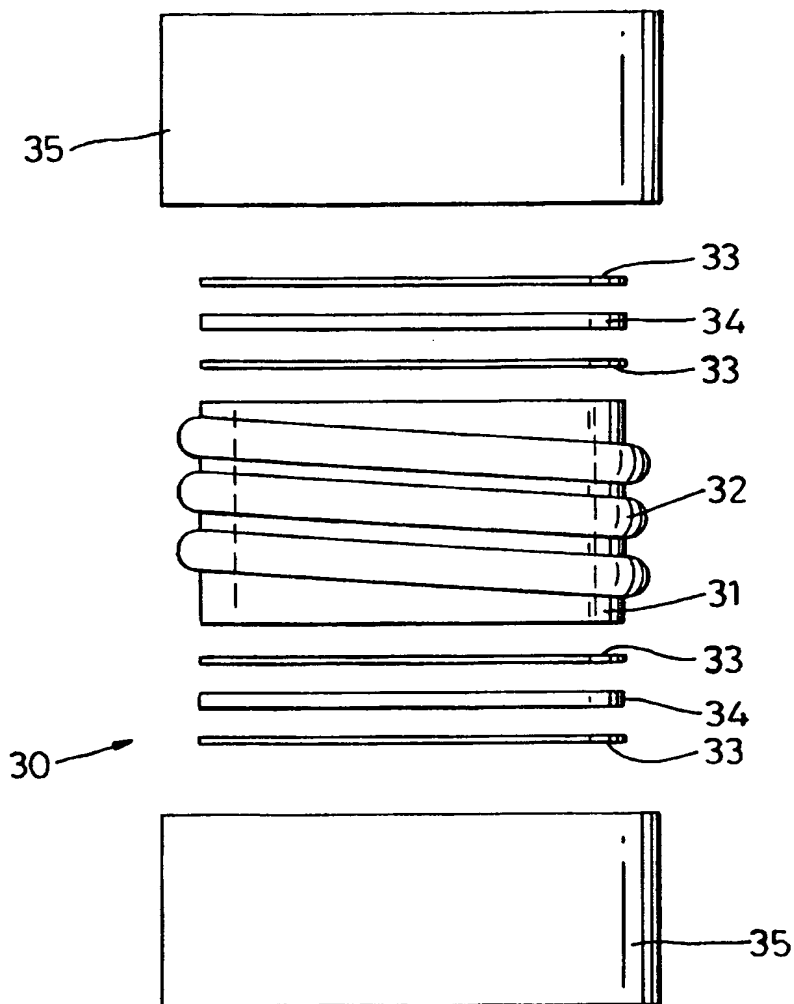
*Fig. 1*



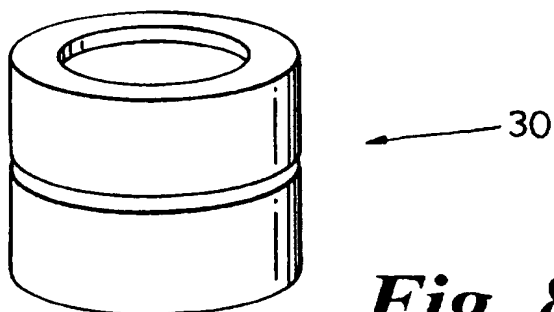
*Fig. 2*

**Fig. 3****Fig. 4****Fig. 5****Fig. 6**

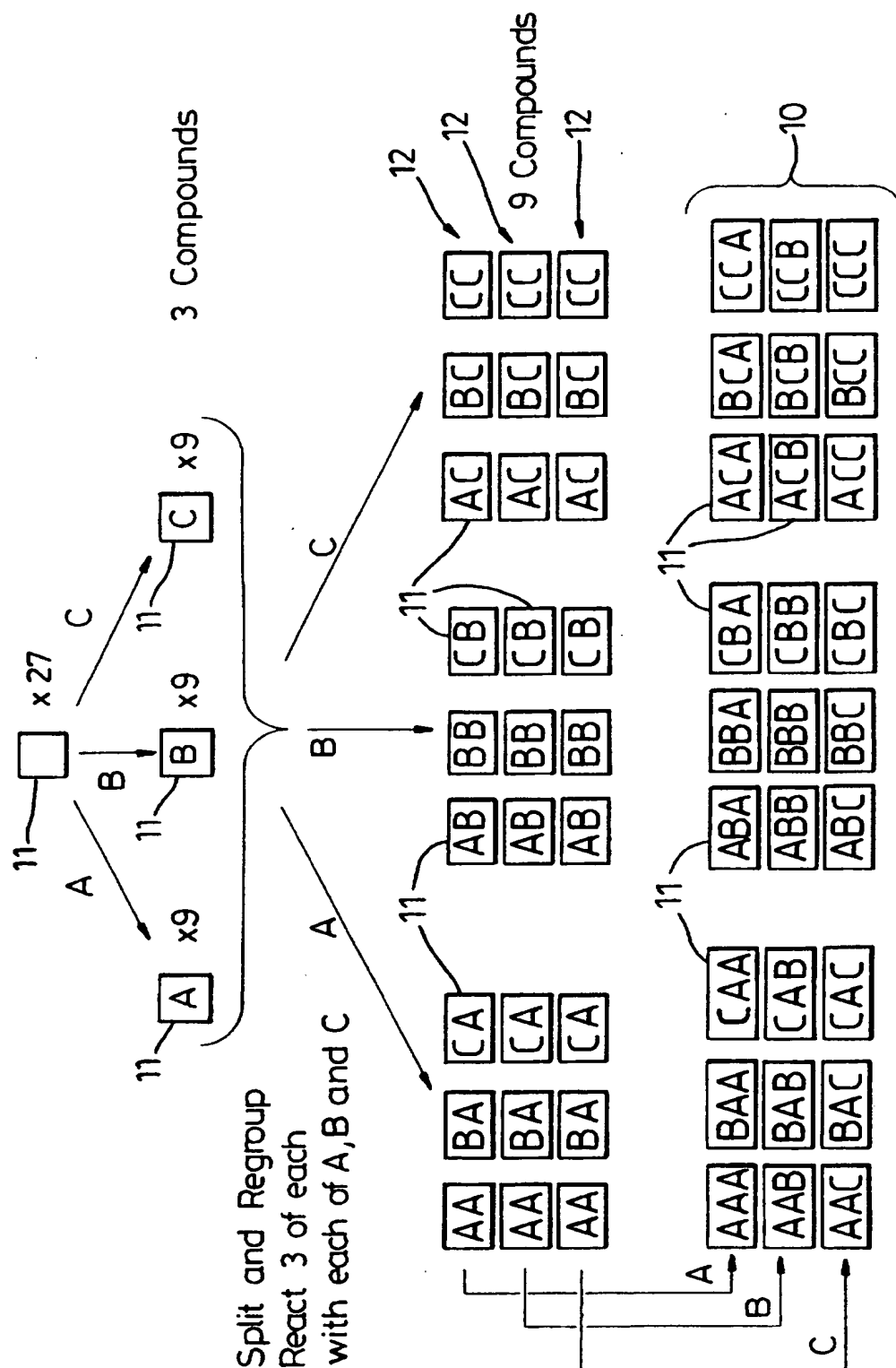
3/4



**Fig. 7**



**Fig. 8**



Library of 27 Compounds

**Fig. 9**



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 97/00496

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 B01J19/00 C07K1/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C12M B01J C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 156 588 A (APPLIED BIOSYSTEMS) 2 October 1985	1-10, 12-14
Y	see page 40 - page 42; claims 1-6; figures 1-5	1-11
Y	--- EP 0 196 174 A (SCRIPPS CLINIC RES) 1 October 1986 see page 21; figure 5B	11
Y	--- FR 2 526 169 A (MOCHIDA PHARM CO LTD) 4 November 1983 see claims; figures ---	1,2,4-8
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

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Date of the actual completion of the international search

13 June 1997

Date of mailing of the international search report

01.07.97

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# INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/GB 97/00496

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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